IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC, Defendants.	C.A. No. 19-2017 (RGA) (SRF) (Consolidated)

DEFENDANTS' RESPONSIVE POST-TRIAL BRIEF ON NONINFRINGEMENT

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I. INTRODUCTION

Exelixis filed this Hatch-Waxman patent infringement suit against MSN, asserting at trial claim 1 of U.S. Patent No. 8,877,776 ("the '776 patent"), which is listed in the Orange Book for Exelixis' cancer drug Cabometyx®. The '776 patent covers a specific crystalline polymorph of the (L)-malate salt of cabozantinib[1] called Form N-2. MSN successfully designed around the '776 patent to create a novel polymorph called Form S, which MSN will use as its API, pursuant to ANDA No. 213878, in its proposed generic version of Cabometyx® ("MSN Tablets").

To prove infringement, Exelixis must show that MSN's Tablets will infringe the asserted claim using at least one of two polymorph characterization methods: ^{13}C SSNMR or XRPD. Exelixis performed ^{13}C SSNMR testing, and MSN performed XRPD testing, on representative samples of MSN's Tablets and API. Each side's experts analyzed the data presented by the other.

Exelixis claims there are three "key issues" in dispute in this case. Op. Br. at 2. But that overlooks the substantial evidence that is not in dispute. It is undisputed that there is no ^{13}C SSNMR or XRPD test performed by either party that provides any evidence of Form N-2 in MSN's Tablets. Indeed, Exelixis does not claim to offer any direct evidence of infringement at all.

Instead, Exelixis claims to rely on circumstantial evidence based on testing of MSN's API on the theory that if Form N-2 is present in MSN's API at the outset, it will remain in the API after it is formulated into MSN's Tablets. But here too, there is no evidence of infringement, because there is no ^{13}C SSNMR or XRPD test performed by either party that provides any evidence of Form N-2 in MSN's API at prescribed storage conditions, *i.e.*, the conditions at which MSN's API are required to be maintained according to its ANDA. Dr. Munson even conceded at trial that ^{19}F SSNMR (an unclaimed method for characterizing polymorphs) testing, which he asserts is more

[1] There is no dispute that the terms "cabozantinib (L)-malate" and "cabozantinib (s)-malate" are synonymous for purposes of this case.

sensitive than ^{13}C SSNMR, failed to provide any evidence of Form N-2 in MSN's API at prescribed storage conditions.

Thus, to make its infringement claim, Exelixis relies on vague assertions that MSN's API is "unstable" relative to Form N-2, and Dr. Munson's testing on MSN's API after he subjected it to extreme, "accelerated" conditions of high temperature (40°C) and high relative humidity (75%) for extended periods of time (up to 8 weeks). But MSN's API will never be exposed to the "perfect storm" of collective conditions selected by Dr. Munson. And well-settled Federal Circuit law makes clear that "the critical inquiry is whether [a tested sample] is *representative* of what is likely to be approved and marketed." *Merck Sharp & Dohme Corp. v. Amneal Pharms. LLC*, 881 F.3d 1376, 1385 (Fed. Cir. 2018) (emphasis added). Therefore, Dr. Munson's testing of adulterated API should be irrelevant to the Court's infringement decision.

Exelixis' post-hoc justifications for Dr. Munson's use of accelerated testing to "ascertain" how MSN's API "will behave in the real world," Op. Br. 3, are also all flawed. First, the entire premise of Dr. Munson's use of these conditions—to *predict* polymorphic stability during the storage life of the product—is faulty, because it ignores that Dr. Munson received (and tested) MSN's Tablets and API that had already been in storage for three years, providing samples of what happens to those products *in reality*. Second, even a cursory review of MSN's batch manufacturing records and the storage conditions required by its ANDA confirms that MSN's API will never be exposed to the Dr. Munson's collective extreme conditions during storage or manufacturing of MSN's Tablets. And finally, while pharmaceutical companies, including Exelixis and MSN, often perform accelerated stability studies pursuant to ICH Guidelines, such testing is primarily designed to test for potential *chemical* instability during the storage of API, which bears no correlation to *polymorphic* instability or conversion. Indeed, the scientific literature explicitly cautions that

accelerated studies are problematic for assessing polymorph stability, because they can artificially cause a phase transformation.

The facts of this case, in which plaintiff's expert relied upon accelerated testing to purportedly predict whether a defendant's polymorph API would convert in storage over time, are remarkably similar to *Lundbeck v. Lupin Ltd.*, which went to trial before Judge Stark last year. 2021 WL 4944963 (D. Del. Oct. 5, 2021). There, the court found that accelerated testing conditions and "results Plaintiffs turn to as indicative of infringement [were] not relevant to the infringement analysis because they [were] not representative" of the API in the defendants' ANDA products to be sold. *Id.* at *99. The same outcome should result here for the same reasons.

As explained in detail below and in MSN's proposed findings of fact, Exelixis failed to meet its burden of showing that MSN will directly or indirectly infringe claim 1 of the '776 patent.

II. BACKGROUND

A. The Asserted Claim

Claim 1 of the '776 patent provides (FOF ¶ 2):

> 1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N′-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (L)-malate salt, wherein said salt is in crystalline Form N-2 and said Form N-2 is characterized by at least one of the following:
>
> > (i) a solid state 13C NMR spectrum with four or more peaks selected from 23.0, 25.9, 38.0, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ±0.2 ppm;
> >
> > (ii) a powder x-ray diffraction pattern (CuKα λ=1.5418 Å) comprising 2θ values at 20.9±0.2 °2θ and 21.9±0.2 °2θ, and two or more 2θ values selected from: 6.4±0.2 °2θ, 9.1±0.2 °2θ, 12.0±0.2 °2θ, 12.8±0.2, 13.7±0.2, 17.1±0.2, 22.6±0.2, 23.7±0.2, wherein measurement of the crystalline form is at room temperature; and/or
> >
> > (iii) an x-ray powder diffraction (XRPD) pattern substantially in accordance with the pattern shown in FIG. 8.

The asserted claim requires that Exelixis prove Form N-2 is present in MSN's Tablets by

using at least one of two characterization methods: ^{13}C SSNMR or XRPD. FOF ¶ 3. Between the two, Dr. Steed explained that XRPD is the "gold standard" in the field of crystallography and more likely to be "definitive in the identification and characterization of polymorphs." Tr. at 284:7-15 (Steed). Dr. Steed's testimony is consistent with independent scientific literature, which teaches that SSNMR "may be looked upon as representing a middle ground" between XRPD and other methods. Tr. 284:18-23 (discussing PTX-0741.21); FOF ¶ 7. The strength of XRPD testing arises from "the fundamental fact [] that x-ray diffraction depends intrinsically upon the arrangement of the molecules within the crystal [pattern]." Tr. 285:3-8; PTX-0741.47. By contrast, the data provided by SSNMR depends on the "molecular environment," which is "unperturbed by crystallization." Tr. 285:9-17. For these reasons, SSNMR is typically used by persons of skill in the art "in conjunction with [XRPD] rather than by itself." *Id*.

B. Novel Forms of Cabozantinib (L)-Malate

Numerous other crystalline forms of cabozantinib (L)-malate have been developed by generic companies, each with their own unique properties. FOF ¶ 17. MSN's development and design-around attempt led to the successful creation of one of these novel forms, called "Form S." Op. Br. at 2. Each crystalline form can be "identified by virtue of its own [XRPD] pattern." Tr. 292:17-22 (Steed). MSN disclosed the unique pattern for Form S in U.S. Patent No. 11,261,160, which characterizes the novel form by XRPD peaks at 8.2, 10.0, and 13.3 ±0.2º 2θ. DTX-0492.18 (Claim 1); FOF ¶ 17. The API manufactured pursuant to MSN's ANDA No. 213878 and used in MSN's Tablets is the Form S of cabozantinib (L)-malate. FOF ¶ 17.

III. LEGAL STANDARD

Direct infringement under Hatch-Waxman is directed toward "what the ANDA applicant will likely market if its application is approved." *Bayer AG v. Elan Pharm. Rsch. Corp.*, 212 F.3d 1241, 1248-49 (Fed. Cir. 2000); *see also Par Pharm. v. Eagle Pharm.*, 2021 WL 3886418, at *8

(D. Del. 2021) ("What [the ANDA applicant] has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur.") Courts "cannot assume that [an ANDA filer] will not act in full compliance with its representations to the FDA." *Id.* (quoting *In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1378 (Fed. Cir. 2011)).

Induced infringement requires a showing that the alleged infringer knew of the patent, knowingly induced the infringing acts, and possessed a specific intent to encourage another's infringement of the patent. *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1328 (Fed. Cir. 2009). The mere knowledge of possible infringement will not suffice to establish intent. *Id*.

IV. ARGUMENT

There is no ^{13}C SSNMR or XRPD test—the methods required by the asserted claim—performed by either party that provides any evidence of Form N-2 in MSN's Tablets. FOF ¶¶ 34-39. Exelixis does not and cannot dispute this. There is also no ^{13}C SSNMR or XRPD (or even ^{19}F SSNMR) test performed by either party that provides any evidence of Form N-2 in MSN's API at prescribed storage conditions—the conditions at which MSN's API are required to be maintained according to its ANDA. FOF ¶¶ 23, 40-46. Again, Exelixis does not and cannot dispute this either. To make its infringement claim, Exelixis relies on testing on MSN's API performed by Dr. Munson after he exposed the API to "accelerated" conditions of high temperature and high humidity for extended periods of time. FOF ¶¶ 47-49. But for the reasons discussed below, MSN's API will never be exposed to these collectively extreme conditions, making Dr. Munson's testing of this adulterated API irrelevant to this Court's infringement decision.

A. Form N-2 was Not Detected in Testing of MSN's Tablets

Dr. Munson performed at least 20 experiments on MSN's Tablets using a variety of techniques: ^{13}C SSNMR and ^{19}F SSNMR, with and without application of a special "relaxation filter," and before and after weeks of exposure to accelerated conditions of 40°C at 75% relative

humidity. FOF ¶¶ 34-37. None of his testing of MSN's Tablets detected the presence of Form N-2. *Id*. As this Court recognized at the end of trial, Exelixis "never could show any [Form] N-2 in the [MSN Tablets] … either now or after extreme conditions." Tr. 859:1-6.

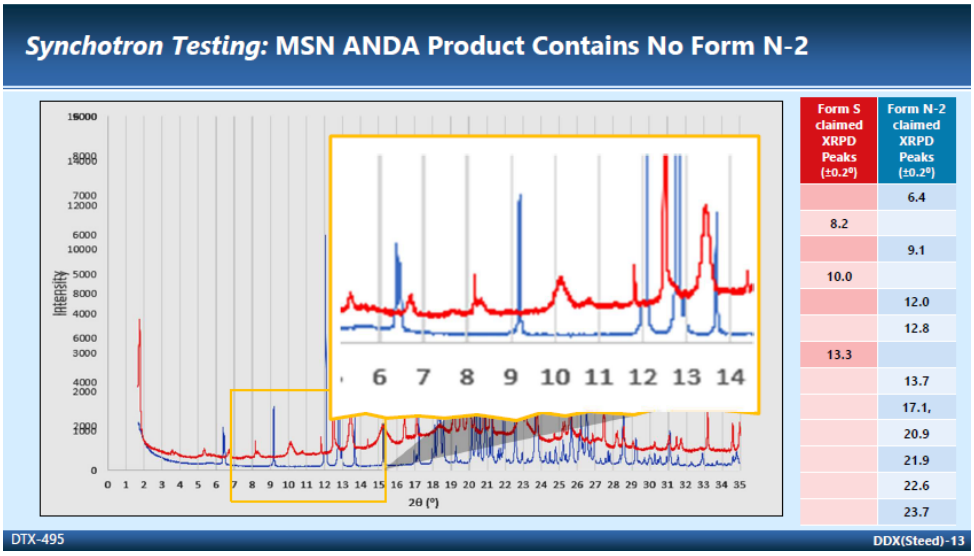
Dr. Munson's failure to find Form N-2 in MSN's Tablets is notable given the many ways he tested the samples. When he could not detect Form N-2 using standard ^{13}C SSNMR, Dr. Munson applied a "relaxation filter" to "filter out" the signal generated by any faster-relaxing Form S from any slower-relaxing Form N-2. Tr. 175:19-176:7 (Munson); FOF ¶ 35. According to Dr. Munson, this technique is useful "when there's more than one crystalline form in a particular sample," because it is designed "to determine the amount of a material that [is] hidden by the presence of another material." Tr. 134:13-18, 102:1-4; FOF ¶ 35. But even after applying the filter, Dr. Munson's ^{13}C SSNMR testing detected no Form N-2 in MSN's Tablets. FOF ¶ 35.

Exelixis speculates that carbon-containing excipients in MSN's Tablet must have "interfered" with the Form N-2 signal (even with a relaxation filter applied). Op. Br. at 5. To be sure, there could be overlap between excipient carbon atom peaks and cabozantinib carbon atom peaks in some portions of the SSNMR spectra. Tr. at 303:9-18. But Dr. Steed explained that this interference would not happen "*in every area*" of the spectra. *Id*. There are many carbon atoms in the cabozantinib molecule, and "in some regions, particularly … the aromatic region, there would not be very much overlap between the excipients and cabozantinib." *Id*. Excipients, therefore, cannot serve as an excuse for Dr. Munson's failure to detect *any* Form N-2 peaks in MSN's Tablets. Tr. 303:24-304:2. Nor can the relative amount of API in the MSN Tablets, given that Dr. Munson claims his SSNMR techniques have the ability to detect the presence of a polymorph that comprises "less than 1 percent of an entire composition." Tr. 220:15-22.

Dr. Munson next performed ^{19}F SSNMR experiments on MSN's Tablets, even though that

is not a method prescribed by the asserted claim. FOF ¶ 3. He claimed that this test would be more sensitive in detecting Form N-2 for two reasons. FOF ¶ 36. First, he explained that ^{19}F SSNMR measures the presence of fluorine-19 atoms, which are "present at a much higher level" than carbon-13 atoms, leading to ^{19}F SSNMR's greater sensitivity. Tr. 131:6-20. Second, unlike carbon—which is present in multiple excipients—fluorine is only found in the cabozantinib API of MSN's Tablets. FOF ¶ 36. Any signal detected by ^{19}F SSNMR would necessarily be from MSN's API and not from excipients. *Id*. Yet despite this purported sensitivity, Dr. Munson detected no Form N-2 in MSN's Tablets. FOF ¶ 37. And while the parties dispute the relevance of testing after exposing MSN's samples to accelerated conditions, as discussed in more detail below, Dr. Munson still could not detect any Form N-2 in MSN's Tablets after subjecting the samples to 40°C at 75% relative humidity for weeks. FOF ¶ 47.

Dr. Munson's results are consistent with the sensitive synchrotron XRPD testing presented by Dr. Steed and gathered from the Advanced Photon Source at Argonne Lab, one of the foremost facilities for XRPD testing in the United States. FOF ¶ 8; Tr. at 348:4-5 (Steed). Dr. Steed analyzed and overlaid the XRPD patterns of MSN's Tablet (in red) against Exelixis' Form N-2 (in blue):



DDX(Steed)-13. Dr. Steed confirmed that characteristic Form N-2 peaks (e.g., 6.4º, 9.1º, 12.0º,

12.8º 2Θ) are not present in the MSN Tablet sample, as seen above. FOF ¶ 38. By contrast, characteristic Form S peaks (*e.g.*, 8.2, 10.0, 13.3º 2Θ) are "readily identifiable" in the MSN Tablet overlaid with MSN's Form S XRPD pattern. Tr. 299:18-25; FOF ¶ 38. And Dr. Munson agreed: no XRPD testing on MSN's Tablets revealed the presence of any Form N-2. FOF ¶ 38.

While Exelixis and Dr. Munson argue that "the ability of *^{13}C SSNMR* to detect Form N-2 in MSN's Tablets (as opposed to the API) was reduced because MSN's API makes up less than 25% of the tablets," Op. Br. at 5 (emphasis added), Dr. Steed explained there is no such concern with *XRPD*, which is highly sensitive to the crystal packing arrangement of a polymorph. FOF ¶ 39. He described the "loading of the API within the drug product" as "quite high," with "a lot of API to observe" for XRPD. Tr. 299:4-10. And Dr. Steed's XRPD overlays clearly show that the characteristic peaks for the MSN Form S API can be detected in the MSN Tablet samples, while the characteristic peaks for Form N-2 are not present. DDX(Steed)-11; DDX(Steed)-13.

Dr. Munson also critiques the use of XRPD because it does "not offer a comparable technique" to the use of a relaxation filter for SSNMR testing, which he claims will "resolve two distinct crystalline forms by filtering out the signal from one of the forms." Op. Br. at 21. For this reason, Exelixis argues that the Form S signal could be obscuring the Form N-2 signal in the MSN Tablet samples. *Id*. at 5, 19. But Dr. Steed explained that this is not a valid concern for XRPD, because there are "region[s] of the x-ray powder diffraction pattern where there is no overlap" between Form S and Form N-2. Tr. 285:22-286:9; FOF ¶ 39. Thus, the "x-ray will reveal whatever peaks are in that region that's free of overlap" without the need to apply any type of filter. *Id*.

There is no dispute that Exelixis failed to present any direct evidence that MSN's Tablets contain Form N-2. Op. Br. 4; FOF ¶¶ 34-39. This should nearly close the door on the infringement inquiry, because while Exelixis offers speculation as to why Form N-2 could not be detected, a

simpler and more persuasive reason remains: Form N-2 is simply not present in the MSN Tablets.

Exelixis' protestations that they are not required to provide direct evidence of Form N-2 in the MSN Tablets misses the point. First, unlike the cases relied on by Exelixis (Op. Br. at 5-6, 22-23), here there was direct evidence in the record proving the lack of Form N-2 in MSN's Tablets. Second, and as explained below, Exelixis' circumstantial evidence argument—i.e., that it can prove infringement of the tablets by showing Form N-2 in the API (Op. Br. at 6)—fails as a matter of fact. Exelixis failed to prove the existence of Form N-2 in MSN's API. Exelixis is free to try to prove up its case using circumstantial evidence (as explained below, that attempt fails as well), but even so, that evidence must still be weighed against the direct evidence to the contrary. In doing so, the evidence presented at trial fails to prove infringement of claim 1.

B. Form N-2 was Not Detected in MSN's API Using the Claimed Testing Methods at Prescribed Storage Conditions.

After failing to present any evidence of Form N-2 in MSN's Tablets—which alone is strong evidence of noninfringement—Dr. Munson next attempted to find Form N-2 in MSN's API. According to Exelixis, "[t]esting of [MSN's] API is sufficient to establish infringement," because "*if* Form N-2 is present in MSN's API, it is necessarily present in MSN's Tablets." Op. Br. at 4-6 (emphasis added). Thus, Exelixis claims that *if* it can demonstrate "that Form N-2 is present in MSN's API *from the outset*" before it is mixed with excipients during manufacture of the tablets, then Exelixis can show "that Form N-2 is necessarily present in MSN's Tablets" because it will "not magically disappear once it enters the tablets." Op. Br. at 5-6, 25 (emphasis added).

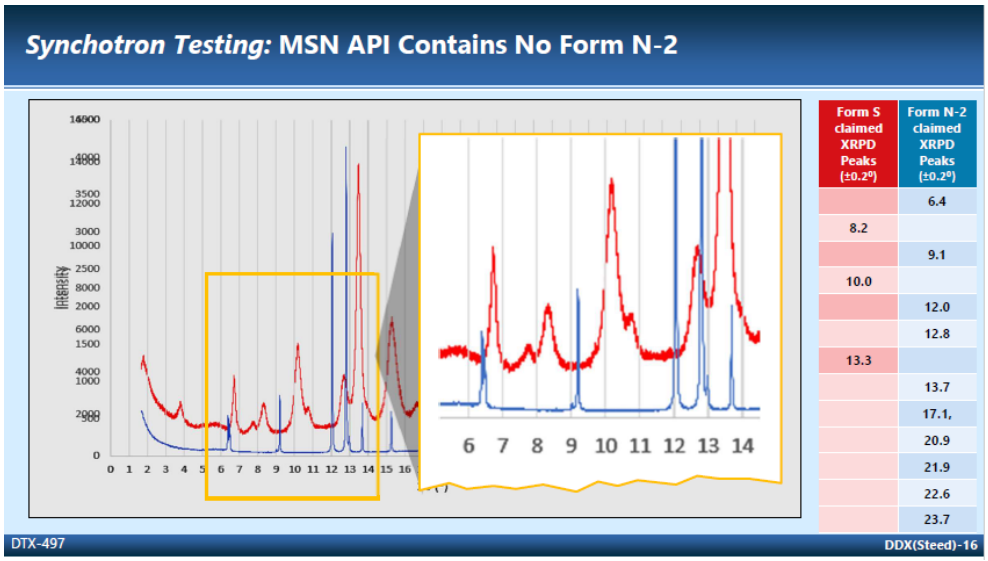
The problem for Exelixis lies not in its logic, but in the facts. Form N-2 is *not* present in MSN's API at the outset, and therefore Exelixis' own paradigm for proving infringement falls apart. FOF ¶¶ 40-46. Dr. Munson did not present any testing data showing Form N-2 in representative samples of MSN's API stored under prescribed conditions *at the outset*, i.e., before

being subjected to accelerated conditions. *Id*. In fact, all of the data collected using the claimed testing methods is to the contrary—it shows no Form N-2 in MSN's API. *Id*.

1. MSN's XRPD Testing Revealed No Form N-2 in MSN's API.

As with MSN's Tablets, Dr. Munson did not perform XRPD testing on MSN's API. FOF ¶ 41. He did, however, review the XRPD data collected by Dr. Steed and MSN's internal XRPD data, and conceded that no Form N-2 was detected in these tests. *Id*. And for good reason—the XRPD testing of record demonstrates that MSN's API consists of Form S, not Form N-2.

Dr. Steed presented XRPD data collected from Argonne lab for both Exelixis' Form N-2 API and MSN's Form S API. Using the demonstrative slide shown below, Dr. Steed overlaid MSN's API (shown in red) with Exelixis' API (shown in blue):



FOF ¶ 41; DDX(Steed)-16. This testing showed that Exelixis' API matched the claimed N-2 peaks (*e.g.*, 6.4º, 9.1º, 12.0º, 12.8º 2Θ), while MSN's API did not. *Id*. In other words, based on this testing, "[t]here's no evidence of Form N-2 at all" in MSN's API. Tr. 305:6-10 (Steed). Dr. Munson did not disagree. FOF ¶ 41. As importantly, this testing confirms the suitability of XRPD to detect Form N-2 in an API sample—as it unambiguously detected Form N-2 in Exelixis' API,

which Exelixis contends contains only Form N-2. The absence of any XRPD data showing Form N-2 in MSN's API is thus telling.

Dr. Steed also presented MSN's internal XRPD testing. Again, that testing did not show any Form N-2 in MSN's API. FOF ¶¶ 25-29. And again, Dr. Munson did not disagree. FOF ¶ 29.

Exelixis discounts MSN's internal XRPD testing by arguing that MSN's release specification does not "prohibit the presence of Form N-2." Op. Br. at 12 (citing PTX-58 (MSN's API Specification)). But this critique is unavailing. Exelixis must prove that Form N-2 is present in MSN's API. Even if the release specification "does not prohibit the presence of Form N-2," that does not help Exelixis *prove the presence* of Form N-2 in MSN's API. For the same reason, Exelixis' cited cases (Op. Br. at 12) actually support MSN. In *Novartis v. Par Pharmaceutical, Inc*., unlike here, the court found that the plaintiff had proven that the defendant's ANDA product contained the claimed excipient. 48 F. Supp. 3d 733, 743-744 (D. Del. 2014). And in *Astellas US LLC v. Hospira, Inc*., like here, plaintiff's "failure of proof necessitate[d] a finding of noninfringement." No. CV 18-1675-CFC, 2022 WL 1591277, at *28 (D. Del. May 19, 2022).

More importantly, the evidence presented at trial showed that MSN's release specification effectively precludes the presence of Form N-2. *Accord Astellas*, 2022 WL 1591277 at *28 (finding noninfringement where release specification excluded the presence of other forms). Dr. Steed explained that MSN's specification does not merely look to four characteristic Form S peaks, but rather requires "comparing the whole [XRPD pattern] to a standard." Tr. 401:2-9 (discussing PTX-118.28). Dr. Steed further confirmed that his understanding was consistent with the testimony of Dr. Reddy, MSN's API Scientist. FOF ¶¶ 19-20.

Dr. Reddy testified that the specification's requirement to "compare the sample [XRPD pattern] with the standard [XRPD pattern]" ensures that the two patterns "match[] fully." Tr.

253:5-10. This matching ensures that no peaks attributable to Form N-2 are present, otherwise the patterns would not fully match. FOF ¶ 20. Dr. Reddy also explained that because MSN's manufacturing method for Form S "has been fully validated," that means the manufacturing process "is consistently producing Form S," as we can see in the API samples tested by both parties at prescribed storage conditions. Tr. 249:13-16. Indeed, Dr. Steed explained the XRPD specification "is an in-process control as part of the well-validated process" that it is "designed to produce Form S time and time again." Tr. 402:9-11.

Thus, Dr. Steed concluded there is no "reason to believe that [] batches of MSN's API could have Form N-2 in them without being detected by MSN." Tr. 401:2-9. This type of release specification is consistent with the defendant's XRPD release specification in *Astellas* that "rule[d] out the observation of any other solid forms." *Astellas*, 2022 WL 159127, at *28 (Plaintiffs failed to show by a preponderance of the evidence that Curia's Form G [API] will likely contain [the claimed] Form A regadenoson."). And in any event, hypothetical MSN API batches that do not comport with MSN's release specification cannot serve as a basis for infringement. *Abbott Lab'ys v. TorPharm*, *Inc*., 300 F.3d 1367, 1373 (Fed. Cir. 2002) ("Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry.").

In short, "MSN's testing of its API," which was initially tested upon manufacture and has continued to be tested "periodically" for "three years and counting" is "consistent with the results []described for the synchrotron test[ing]" that shows only Form S is present, and no Form N-2, in MSN's API. Tr. 306:6-18 (Steed). Thus, using the XRPD data of record—the "gold standard" for identification of a polymorphic form—both Dr. Steed and Dr. Munson agreed that no Form N-2

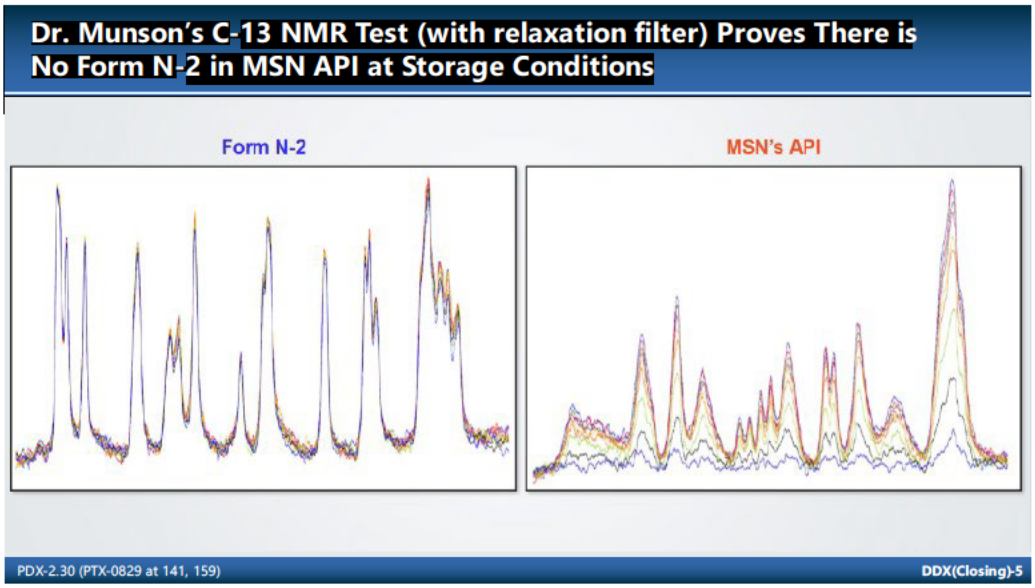
was detected in MSN's API. Tr. 284:7-8; FOF ¶¶ 25-29, 41.

2. Dr. Munson's ^{13}C SSNMR Testing Confirmed There is No Form N-2 in MSN's API at Prescribed Storage Conditions.

Dr. Munson's ^{13}C NMR testing—the other way to determine infringement under the asserted claim—likewise did not detect any Form N-2 in MSN's API at prescribed storage conditions. FOF ¶¶ 42-43. Indeed, Dr. Munson admitted that after analyzing MSN's API with "^{13}C NMR, at standard conditions," both with and without a relaxation filter, "[he] did not determine any direct peaks associated with Form N-2" in MSN's API. Tr. 176:20-177:11. In other words, Dr. Munson's ^{13}C NMR testing failed to provide any evidence of infringement of claim 1.

With respect to testing of MSN's API stored at prescribed conditions and without applying a relaxation filter, Dr. Munson admitted that the claimed Form N-2 "is just simply not detected in th[is] spectra for MSN's API." Tr. 133:24-134:1. Dr. Munson further confirmed that the testing showed that MSN's API and Form N-2 are "quite different." Tr. 133:13-19 (discussing PTX-767 and PTX 785A); FOF ¶ 42.

Because he did not initially detect Form N-2 in MSN's API with ^{13}C SSNMR, Dr. Munson explained that he then "applied … a relaxation filter to MSN's samples" to determine if Form N-2 is "present at a small level." Tr. 133:24-134:18. Like the relaxation filter described above for testing MSN's Tablets, Dr. Munson explained that applying the filter allows him to detect one compound "in the presence of another." Tr. 134:13-14. Said another way, the SSNMR signal for "MSN's API material will essentially disappear" when applying the filter, but the Form N-2 signal will remain. Tr. 136:13-138:13 (describing PTX-0829 at 141, 159). But Dr. Munson's spectra, reproduced in MSN's demonstrative below, confirms no Form N-2 is present in MSN's API:



DDX(Closing)-5. Even after applying the relaxation filter to "get rid of" the Form S signal (see the dark blue line in the right-hand call-out), Dr. Munson conceded that he still could not detect Form N-2 in MSN's API. Tr. 138:2-4; FOF ¶ 42. Dr. Munson admitted that "when we applied the filter to MSN's material … we saw a spectrum that basically doesn't really look like … the Form N-2." Tr. 138:21-24. Dr. Steed agreed there was no sign of Form N-2 and explained that "[i]f form N-2 were present in this sample," then after applying the relaxation filter, "you would expect to see those Form N-2 signals, [but] [w]e don't see them." Tr. 309:10-16; FOF ¶ 42.

Exelixis also nonsensically faults MSN for not conducting any SSNMR testing of its own. Op. Br. at 21. Of course, Exelixis has the burden of proving infringement, and MSN has no obligation to conduct any testing at all. Nevertheless, Exelixis suggests that MSN's "failure to do so is telling." *Id.* MSN agrees. It tells one that not only did Exelixis fail to carry its burden of proof with its own SSNMR testing, but that Dr. Munson's SSNMR testing at prescribed storage conditions actually *supports* MSN's defense. There was no reason for MSN to conduct more.

Thus, the evidence at trial was undisputed that the ^{13}C SSNMR data for the representative samples of MSN's API under prescribed storage conditions, both with and without the application

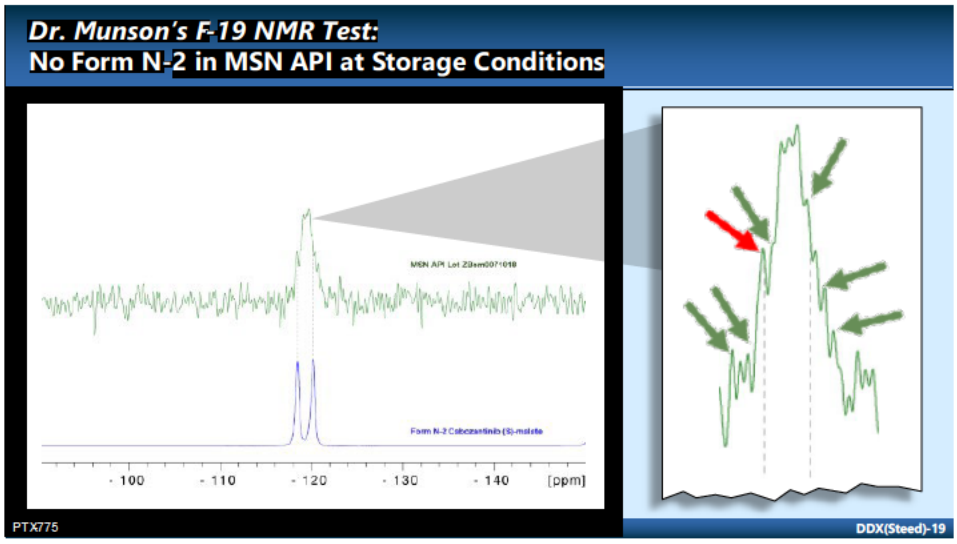
of a relaxation filter, did not show the presence of Form N-2 in MSN's API. FOF ¶ 42

C. Testing of MSN's API Using Unclaimed ^{19}F SSNMR Methods Does Not Support Infringement

In light of its failure to prove Form N-2 is present in MSN's API under prescribed storage conditions using either of the two testing methods required by the asserted claim, Exelixis attempts to salvage its infringement claim by relying on ^{19}F SSNMR testing. But the data presented at trial fails to support Exelixis' claim. Indeed, the ^{19}F SSNMR testing conducted at 0 weeks (i.e., before MSN's API was subjected to accelerated conditions) did not show the presence of Form N-2. FOF ¶¶ 44-46. Exelixis now seems to concede that point and has instead shifted to a new theory based on the "rate of conversion" after exposure of MSN's API to accelerated conditions. Both fail.

1. Dr. Munson Conceded that His ^{19}F SSNMR Testing Did Not Detect Form N-2 in MSN's API at Prescribed Storage Conditions

At trial, Dr. Munson presented an ^{19}F SSNMR spectrum obtained using a relaxation filter on one lot of MSN's API stored at prescribed storage conditions, which he then "vertically expanded by 16 times." Tr. 161:19-162:6 (citing PTX-783). He identified a feature in this zoomed-in spectrum and stated, although "the peak looks strange," he "can see where the Form N-2 peak is present on the left" (Tr. 161:24-162:3), shown by the red arrow in Dr. Steed's demonstrative:



DDX(Steed)-19 (citing PTX-775) (annotated).

On cross-examination, however, Dr. Munson conceded that he could not attribute this feature to Form N-2. For instance, when asked whether he saw any peaks attributable to Form N-2, Dr. Munson clarified, stating "[w]ell, not exactly, no," this feature is only "the suggestion of a peak." Tr. 226:12-17; FOF ¶¶ 45-46. And Dr. Munson conceded that he never performed any signal-to-noise analysis to objectively compare his "suggestion of a peak" (red arrow) to the other nearby features (green arrows) in this noisy spectrum. FOF ¶ 46. In any event, a "suggestion" of a single peak is plainly insufficient to establish the presence of a polymorphic form.[2]

Given Dr. Munson's admission, not surprisingly, Exelixis now tacitly concedes that his ^{19}F SSNMR testing conducted at 0 weeks of exposure to accelerated conditions did not prove the presence of Form N-2 in MSN's API. *See* Op. Br. at 19 (arguing that a different crystalline form "interfered with the Form N-2 signal at 0 weeks")[3]; *see also id.* at 4 (conceding that Dr. Munson's ^{19}F SSNMR testing data "demonstrated the presence of Form N-2 *as early as 1 week under accelerated conditions*.") (emphasis added).

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[2] At trial, Dr. Steed showed comparable ^{19}F SSNMR data on other lots of MSN's API that Dr. Munson did not present. FOF ¶ 46. Dr. Steed explained that these other samples produced "less noisy spectra," which is "particularly telling" because the "noise feature" that Dr. Munson identified as a "suggestion of a peak" "disappeared" in these less noisy spectra. Tr. 313:8-11. The feature disappeared "because the signal-to-noise" ratio, a measurement to distinguish a true signal from experimental noise, "is better" for these other lots of API. 313:8-11 (Steed). Thus, Dr. Steed concluded that the feature is merely noise. Tr. 313:8-11. After all, "[a] scientist, looking for repetition and reproducibility, would not attribute noise in a single diffractogram that did not recur in [the] testing to be [Form N-2] material." *Lundbeck*, 2021 WL 4944963, at *28. Dr. Steed therefore concluded that there is no "evidence of any testing performed on MSN's API at recommended storage conditions that shows [Form] N-2 in [MSN's] API." Tr. 313:18-21.

[3] Dr. Munson claims that the alleged interference was caused by "the presence of an additional, unidentified polymorphic form of cabozantinib." Op. Br. at 5, 19. But Dr. Munson conceded that it was not Form N-2. Tr. 175:19-21 ("I detected another form … but no, I did not detect N-2."); *see also* Tr. 310:17-19 (Steed) ("We don't know if [the unidentified polymorphic form] is Form S" signal that "survive[d] the [relaxation] filter" "or something else."). Thus, it has no bearing on the infringement analysis.

2. Dr. Munson's "Rate of Conversion" Theory is Unsupported by the Record and Does Not Prove the Presence of Form N-2 in MSN's API at Prescribed Storage Conditions

Without any test results detecting Form N-2 at prescribed storage conditions, Exelixis now pivots and argues "that Form N-2 [i]s present in MSN's API from the outset" based on purported conversion rate data across three lots of MSN's API exposed to accelerated conditions. Op. Br. at 19. But Exelixis' conversion rate theory cannot save its infringement case and its utter lack of any testing showing Form N-2 in MSN's API prior to being subjected to accelerated conditions.

Exelixis argues that "Dr. Munson was able to determine that Form N-2 was present in MSN's API from the outset by comparing the *rate of conversion* to Form N-2 over time (*i.e.*, starting at one week) across [three] lots of MSN's API" exposed to accelerated conditions. Op. Br. at 19. Dr. Munson's theory goes: "[i]f there was no Form N-2 in any of the [three MSN API] batches at the outset, the rate of conversion in [those lots] would have been identical" after exposure to accelerated conditions.[4] *Id.* at 20. According to Dr. Munson, there was a "difference in conversion rates across lots," leading him to conclude "there were different amounts of Form N-2 *initially* present in the three lots." *Id.* at 19-20.

Despite the (newly) professed importance of Dr. Munson's rate of conversion theory to Exelixis' infringement claim, Dr. Munson did not actually present the Court with any ^{19}F SSNMR data from two of the three MSN API lots at trial. Nor did he offer any comparison or overlay of the spectra collected from different lots to support his opinion. Indeed, Dr. Munson offers nothing more than an *ipse dixit* conclusion that the rates of conversion across the three lots of MSN API vary by any meaningful degree.

[4] Dr. Munson has not identified any scientific literature supporting his theory that the rate of polymorph conversion across lots of API will be identical if exposed to similar conditions. *See Lundbeck*, 2021 WL 4944963, at *94 ("[T]he Court was not persuaded by the testimony of Dr. Myerson, who cited no literature to support his opinion").

But Dr. Munson's opinion is directly contradicted by his testimony. His rate of conversion theory necessarily refers to a measure of how *the quantity* of Form N-2 changes over time. But Dr. Munson repeatedly admitted that he *never quantified* the amount of Form N-2 in any lot of MSN's API exposed to his accelerated conditions. Tr. 179:3 ("I did not quantify it, no"), 179:9-10 ("I didn't perform quantitation experiments.") When asked whether he *could* quantify the amount of Form N-2 in MSN's API exposed to accelerated conditions, Dr. Munson admitted he "showed a paper where we did that," but "[i]t's not an easy thing to do" and his testing here was "all about detection." Tr. 222:1-10; FOF ¶ 49.

Because Dr. Munson never measured how much Form N-2 was purportedly present in any sample of MSN API, he can have no way of calculating whether the rates of conversion, i.e., the *change in the quantity* of Form N-2, were appreciably different across different lots of API. Dr. Munson contends that "the spectra were plotted so that they're quantitative with respect to each other." Tr. 221:22-25. But aside from his failure to actually present those spectra at trial, he offers no calculation, analysis of statistical significance, or other objective measure to establish any true or meaningful difference between the lots of MSN API exposed to accelerated conditions.

Because Dr. Munson's rate of conversion theory based is plagued by "speculative data," it "cannot sustain [Exelixis'] burden of proof" on infringement. *See Brigham & Women's Hosp., Inc. v. Perrigo Co.*, 761 F. App'x 995, 1003-04 (Fed. Cir. 2019).

D. Testing of MSN's API at Accelerated Conditions is Irrelevant to the Infringement Inquiry

Lacking any direct or credible evidence of Form N-2 in MSN's Tablets or MSN's API at the outset, Exelixis relies on Dr. Munson's "accelerated" testing as circumstantial evidence of what may happen to the API in MSN's Tablets over time. But in reality, Dr. Munson's accelerated testing intentionally changed MSN's API into an entirely different product—one that will never

be sold or distributed by MSN. Because Dr. Munson's adulterated API is not representative of "what the ANDA applicant will likely market if its application is approved," the Court should not consider his accelerated testing in its infringement analysis. *Bayer*, 212 F.3d at 1248-49; *see also Merck*, 881 F.3d at 1385 ("[T]he critical inquiry is whether [the API sample] is representative of what is likely to be approved and marketed."); *Glaxo, Inc. v. Novopharm, Ltd*., 110 F.3d 1562, 1570 (Fed. Cir. 1997) ("What is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists.").

1. Dr. Munson's Accelerated Conditions Created the "Perfect Storm" for Polymorph Conversion in MSN's API

The premise of accelerated testing, according to Dr. Munson, is that "if [a polymorph] converts under the accelerated conditions, it will also convert under the real-world conditions." Tr. 141:13-15. But Dr. Munson's premise is incorrect, especially under the accelerated conditions he applied in this case.

The scientific literature cautions against using accelerated conditions as a predictor of polymorphic stability. For example, one seminal textbook on polymorphism in pharmaceutical solids cautions that accelerated testing—which Dr. Steed explained is primarily designed to test for potential *chemical* degradation over time—"can become problematic" for the "kinetics of phase transformation." FOF ¶ 16; DTX-484.050 (Brittain). The Brittain reference further teaches that the temperatures reached in stress testing "may exceed the temperature of a polymorphic phase transition," triggering conversion of one polymorph to another. DTX-484.050. Or the relative humidity may cause a "solvatomorphic transition." DTX-484.050. Or the accelerated conditions may "increase [the] molecular mobility in the solid," making a phase transition "more rapid." DTX-484.050. Dr. Steed summarized the reference as teaching that a polymorph "transformation that might not occur in ambient conditions or under storage conditions might be brought about by

increase in temperature, or other change in conditions." Tr. 315:15-16.

Dr. Munson did not dispute the teachings of the Brittain reference at trial, but nevertheless subjected MSN's API to extreme accelerated conditions that included nonstop exposure of (1) unformulated API, (2) to 40°C, (3) at 75% relative humidity, (4) for periods up to eight weeks. FOF ¶ 33. Dr. Steed explained how each of the test conditions selected by Dr. Munson makes polymorph conversion of MSN's API more likely over time: (1) unformulated API lacks stabilizing excipients that would be present in MSN's Tablets; (2) elevated temperatures are known to cause polymorph phase transformations; (3) water vapor from elevated humidity can alter the hydration state or make molecules within a crystal form more mobile and prone to phase transition; and (4) the length of exposure provides additional opportunity for phase transitions to occur and grow. FOF ¶¶ 16, 22, 48.

Dr. Munson also conducted his accelerated testing in "unsealed" vials, exposing MSN's API directly to the 40°C and 75% relative humidity atmosphere. Tr. 192:16-18 (Munson). As discussed below, this drastically deviated from MSN's API container closure system, which includes moisture barriers, desiccants, and other protections, as well as ICH Guidelines for accelerated testing, which require the sample be "packaged in a container closure system that is the same as or simulates" the proposed packaging. FOF ¶ 23; PTX-0739 at 8, 13.

Collectively, Dr. Munson's accelerated conditions created what Dr. Steed described as a "perfect storm" of "ultimate stress" on the polymorphic form of MSN's API. Tr. 318:4-10. It should be no surprise, then, that Dr. Munson was able to artificially cause some unquantified amount of MSN's API to convert to another form after eight weeks of exposure.[5] But Dr. Munson's

[5] However, the Court should consider how Dr. Munson arrived at his infringement opinion after exposing MSN's API to accelerated conditions for only four weeks. When Dr. Munson used

extreme accelerated conditions and "results Plaintiffs turn to as indicative of infringement [] are not relevant to the infringement analysis because they are not representative" of MSN's API in the MSN Tablets that will be sold. *Lundbeck*, 2021 WL 4944963, at *99; *see also Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1187 (Fed. Cir. 2014) ("[T]he composition of the generic product proposed in Barr's ANDA is significantly different from the compositions tested in Alcon's study."); *Doorking, Inc. v. Sentex Sys., Inc.*, 19 F. App'x 872, 878 (Fed. Cir. 2001) ("[A]n accused device does not infringe if it does not infringe in its normal configuration, even if it may be altered into an infringing configuration under unusual circumstances.").

Exelixis asserts a series of reasons for why Dr. Munson's accelerated testing should be relevant to predicting how MSN's API will behave in the real world over time, including during API and tablet manufacturing, transportation, and storage (before and after the tablets leave MSN's possession). Each one fails to support Exelixis' infringement claim.

2. Dr. Munson's Accelerated Conditions Do Not Predict How the Polymorphic Form of MSN's API Will Behave "Over Time"

Exelixis first argues that Dr. Munson's accelerated conditions are relevant to the "real world" behavior of the drug substance in MSN's Tablets, because they predict how MSN's API will behave in storage "over time." Op. Br. at 3; *id.* at 14-15, 17. But even assuming accelerated testing is appropriate for *predicting* polymorphic stability—and it is not[6]—the entire premise of

objective peak-picking software on his ^{13}C SSNMR data, the computer identified only 3 of 4 peaks required by the asserted claim (at 69.6, 177.1, and 179.9 ppm). Tr. 336:24-337:15 (Steed); 225:6-11 (Munson); 149:18-25 (Munson). To reach his infringement opinion, Dr. Munson then "manually" picked two more peaks (at 25.9 and 180.3 ppm) that coincided with ones claimed by the '776 patent. Tr. 336:24-337:15 (Steed). However, he failed to perform any signal-to-noise analysis or any other impartial, replicable measure to confirm the features he manually identified represented true peaks in the spectrum. Tr. 228:1-16 (Munson) ("I didn't specifically measure the signal-to-noise ratio"); 311:4-312:9 (Steed). This is further evidence of the results-driven methodology Dr. Munson applied at every turn to reach his preordained infringement opinion.

[6] *See* Sections IV.D.1, IV.D.5.

this argument ignores that Dr. Munson received (and tested) aged samples of MSN's Tablets and API that had already been stored for years, reflecting what happens to them *in reality*. FOF ¶ 30.

MSN's Tablets have a shelf life of 18 months or two years, depending on the dosage strength. FOF ¶ 24. MSN's API has a proposed "retest" period of 30 months. Tr. 116:5-10 (Munson); PTX-125.29. The MSN Tablet and API samples Dr. Munson tested were older than either of those dates—about three years old by the time he tested them. FOF ¶ 30. It was, therefore, not necessary to use accelerated conditions to evaluate how the MSN Tablets or API may be expected to behave over the storage life of the product. Dr. Munson could (and did) simply test the aged products at the prescribed storage conditions to determine whether any Form N-2 was present, and he found none. FOF ¶¶ 34-39. As Dr. Steed explained, "we don't need to run accelerated tests because we [] have data on the actual tests" run on three-year old samples of MSN's Tablets. Tr. 328:14-23. Because "these samples are sufficiently old," if "conversion to Form N-2" were "to occur … [w]e would see the evidence for Form N-2" in the SSNMR and XRPD data run at storage conditions. 302:7-22.

Exelixis responds that three years of storage is not enough. Because MSN's API does not have an expiration date, but rather must be "retested for stability" after 30 months, Exelixis contends that Dr. Munson's accelerated conditions are necessary "for observing the behavior of the API over its entire shelf life, which may be significantly longer than its initial retest period." Op. Br. at 18. Of course, this speculation is not based on any record evidence suggesting that—once approved by FDA—MSN will stockpile commercial batches of API for more than 30 months before manufacturing its ANDA product. And Exelixis has offered no reason to believe that Form S in MSN's API, stable for three years at storage conditions, would suddenly convert after 30 months under unchanged storage conditions. Dr. Steed explained that because "there's no evidence

of Form N-2 in MSN's API" after three years of storage, "there's no reason to think that … it would begin to convert [to Form N-2] at any point" "after three years" "when kept in the storage conditions." Tr. 305:24-306:5.

Exelixis cannot meet its burden of proof with mere speculation that the API will suddenly start to convert after three years of no conversion. *See Glaxo*, 1997 WL 355339 *2 ("In this case, Glaxo similarly argued that Boehringer's filing of the ANDA infringed the claims of the Form 2 RHCI patents by virtue of the '*potentiality*' that the product Boehringer sought to market following approval *might* contain certain amounts of Form 2 RHCI.") (emphasis added).

3. MSN's API Will Not Be Exposed to Dr. Munson's Accelerated Conditions During Manufacturing

Exelixis argues that Dr. Munson's accelerated conditions are relevant to the "real world" behavior of the drug substance in MSN's Tablets, because they reflect conditions that MSN's API will be exposed to during the API and tablet manufacturing process. Op. Br. at 3 n.3, 4-5, 15, 17-18. But MSN's API is *never* subjected to the *combination* of high temperatures, high moisture, and time of exposure during Dr. Munson's accelerated testing, making this justification inapposite.

As an initial matter, Exelixis repeatedly points to a drying step during the manufacturing of MSN's API (not the MSN Tablets) where it claims the intermediate drug substance is "exposed to 55-60°C under high humidity for ~8 hours."[7] Op. Br. at 17. Even accepting Dr. Munson's flawed premise that accelerated conditions reflect what MSN's API will go through during manufacturing, the MSN API samples Dr. Munson received had *already* been subjected to 55-60°C for ~8 hours *in order to be made*. FOF ¶ 21; Tr. 186:14-22 (Munson). Of course, if this step in the preparation

[7] Contrary to Exelixis' claim, this step does not take place "under high humidity." In the preceding step, the intermediate is washed with "[m]ethylene dichloride," a type of organic solvent. PTX-0129 at 76. The intermediate is then loaded into a vacuum oven to dry the material of the methylene dichloride. *Id*. Neither water nor high humidity is introduced in these steps.

of MSN's API somehow caused Form N-2 to materialize, then it would have been present in the samples Dr. Munson received (and tested) *before* he subjected them to his accelerated conditions. Tr. 327:20-328:3 (Steed) ("It's not necessary to see what would happen to that material under further stress because it's already been stressed.") But as discussed above, Dr. Munson never detected any Form N-2 in MSN's API samples before exposing them to his accelerated conditions.

Dr. Munson's accelerated conditions also bear no relationship to the conditions MSN's API will be exposed to during tablet manufacturing, as Dr. Steed explained using MSN's ANDA and manufacturing batch records. MSN's chart summarizing the differences between Dr. Munson's testing and the tablet manufacturing steps that Exelixis claims justifies his accelerated conditions is below, DDX(Closing-13):

Dr. Munson's "Accelerated" Conditions Do Not Mimic MSN's ANDA Product Manufacturing Process

Dr. Munson's Accelerated Conditions	MSN's Wet Granulation Step	MSN's Drying Step	MSN's Coating step
API only	API + excipients	API + excipients	API + excipients
40°C	21-25°C	28-40°C	35-45°C
75% RH	45-55% RH	Ambient	Ambient
4-8 weeks	~3 minutes	<2 hours	<3 hours

Munson Opening, ¶ 8283; DTX-0490.40, 44, 46, 48, 52, 60, 75, 161-163, 167 13

Exelixis cannot dispute that these conditions are drastically different. First, during each of MSN's wet granulation, drying, and coating steps, MSN's API is already mixed with excipients before exposure to the relevant conditions. FOF ¶ 22. By contrast, Dr. Munson exposed pure MSN API to elevated temperatures and moisture during his accelerated testing. FOF ¶ 33. Dr. Steed explained that this is an important difference, because excipients "can act to stabilize an API, both

chemically and polymorphically." Tr. 316:22-317:1.

Dr. Steed also identified significant differences in the temperature conditions. While Dr. Munson exposed MSN's API to 40°C, MSN's temperature specification for its wet granulation step is only "21 - 25°C." FOF ¶ 22; DTX-490 at 34. For the drying step, MSN's specification is "28 - 40°C," but the actual recorded temperature in MSN's batch records never exceeded 30°C. *Id*. And while MSN's final tablet coating is applied at approximately 40°C, it is the "compressed tablet cores of API plus excipients" that is exposed to this temperature for less than three hours, and not the unformulated API for a period of weeks. *Id*.; Tr. 323:3-14 (Steed).

Likewise, there are differences in the amount of moisture exposure between Dr. Munson's accelerated testing and MSN's tablet manufacturing. While Dr. Munson exposed MSN's API to constant 75% relative humidity, MSN's specification for its wet granulation step is 45-55% relative humidity, and the subsequent drying step is performed at ambient conditions. FOF ¶ 22. Exelixis argues that wet granulation actually exposes MSN's API to 100% moisture when water is added, but this step is only three minutes long, after which the "humidity is being reduced by the air being sucked through and the water being removed" during drying. Tr. 321:24-322:6 (Steed). MSN's final coating step is also performed at ambient conditions, which is a lower relative humidity than Dr. Munson's 75% accelerated condition. Tr. 323:8-10 (Steed).

Finally, the length of exposure to elevated heat and humidity between Dr. Munson's testing and MSN's Tablet manufacturing is critically different. Dr. Munson conceded that his weeks-long *constant* exposure of MSN's API to *all* of his accelerated conditions during accelerated testing "[i]s substantially longer" than the "about four hours" *collective* exposure of MSN's API to at least *one* of his accelerated conditions during the tablet manufacturing process. Tr. 197:14-22.

Exelixis contends that MSN "unduly" focuses on comparing Dr. Munson's accelerated

conditions to MSN's Tablet manufacturing process. Op. Br. at 15. But it was Dr. Munson who claimed at trial that his accelerated conditions were meant to be "representative" of MSN's "manufacturing conditions." Tr. 141:1-6. Indeed, that would be the only way for Dr. Munson's accelerated testing to have even arguable probative value as circumstantial evidence. But because the "perfect storm of stresses" Dr. Munson used in his accelerated testing differ substantially from the conditions prescribed by MSN's manufacturing process, "they are no way relevant as a predictor of polymorph stability … because they don't reflect the conditions that th[e] material will be subjected [to]." Tr. 328:8-13 (Steed).

4. MSN's API Will Not Be Exposed to Dr. Munson's Accelerated Conditions During Storage or Transport

Exelixis also argues that Dr. Munson's accelerated conditions are relevant to the "real world" behavior of the drug substance in MSN's Tablets, because they predict how MSN's API and Tablets will behave under storage and shipping conditions, where exposure to high temperature and humidity "*may* occur." Op. Br. at 3 n.3 (emphasis added); *id.* at 15 n.10. But Exelixis' conjecture is contradicted by the strict storage conditions prescribed by MSN's ANDA.

According to MSN's ANDA, the API will be "[p]reserve[d] in well closed containers … and protect[ed] from moisture." PTX-123.25; *see also* PTX-58.2. Dr. Steed described this "extremely thorough container closure system" with "around five sets of layers of closure," including a series of opaque (to stop degradation caused by ultraviolet light), low-density polyethylene bags purged with nitrogen and silica desiccants (to stop degradation caused by moisture), placed into a high-density polyethylene container. FOF ¶ 23. Dr. Munson conceded that this container closure system was "designed to prevent the MSN API, when stored, from being exposed to the elements like moisture." Tr. 194:7-10. MSN's API will also be stored under refrigerated conditions, at 2-8ºC. FOF ¶ 23.

After MSN's API is formulated into MSN's Tablets, MSN's ANDA provides that the drug product will be stored at room temperature (20°C to 25°C) and at ambient humidity. FOF ¶ 24; PTX-899 at 27. The drug product will be packaged into and stored in a sealed bottle so that the material is not exposed to atmosphere or extreme temperatures. *Id*. Inside the bottle will also be a silica desiccant to absorb moisture. *Id*.

There can be no dispute that the storage and shipping conditions for MSN's API and Tablets bear no relationship to the accelerated conditions used by Dr. Munson. While Exelixis appears to concede that storage of MSN's API and Tablets is controlled while they are in MSN's possession, it speculates that "precise temperature and humidity controls" "may" not be possible during "storage in warehouses," "on pharmacy shelves," "or in patients' homes." Op. Br. at 3 n.3, 15. But Exelixis does not cite any record evidence supporting this conjecture or specifying the purported temperature, humidity, or other "wide variety of conditions" that Exelixis claims MSN's Tablets will be exposed to over time after they leave MSN's possession. Op. Br. at 15. Certainly, Exelixis presented no evidence at trial suggesting that MSN's Tablets will be exposed during transport or storage to the extreme conditions used by Dr. Munson during accelerated testing.

5. Dr. Munson's Use of Accelerated Conditions for His Infringement Analysis is Not Supported by International Guidelines or Industry Practice

To justify Dr. Munson's use of accelerated testing, Exelixis relies heavily on the argument that he is simply following international guidelines and standard industry practice to determine "how a drug will behave in the real world." Op. Br. at 14; *see id.* at 15-17. Setting aside that Dr. Munson had access to and tested aged samples of MSN's Tablets and API that were already exposed to real-world storage conditions, Exelixis has failed to establish that accelerated testing is recommended to predict *polymorph* stability in storage as opposed to *chemical* stability. FOF ¶¶ 12-16, 34-39. And even if one were to accept that accelerated testing is prescribed by international

guidelines as an accurate predictor of polymorph stability in storage, Dr. Munson *failed to follow the guidelines* in his testing. FOF ¶¶ 9-11, 33, 48.

First, Exelixis acknowledges that there is a difference between chemical instability, which "refers to MSN's API transforming into a different compound," and polymorphic instability, which "refers to the tendency of MSN's API to convert to other crystalline forms." Op. Br. at 9 n.5 (citing Tr. 329:9-14 (Steed)). Yet at trial and throughout its opening brief, Exelixis repeatedly conflates the two, suggesting that purported evidence of the former correlates to evidence of the latter. This is incorrect. Dr. Steed provided unrebutted testimony that a compound's chemical stability has no relationship to its polymorph stability—"they're two totally different things." Tr. 329:9-18; *see also id.* at 329:9-14 ("Chemical stability means transforming to a different molecule. Whereas polymorph stability is about change in the crystal packing arrangement of the same molecule."); FOF ¶¶ 12-16. Dr. Steed explained that if an API experiences chemical degradation at accelerated conditions, that does not mean that polymorph conversion is also likely to happen. FOF ¶ 12, 18. Dr. Munson did not offer any contrary testimony.

Exelixis posits, "If accelerated conditions are irrelevant to the long-term stability of MSN and Exelixis' respective APIs (as MSN suggested at trial), why does the FDA require them? Why did both MSN and Exelixis use them during development of their respective cabozantinib products?" Op. Br. at 16. But MSN has never argued that accelerated testing is irrelevant to long-term *chemical* stability. FOF ¶ 12. As Dr. Steed explained, such testing *must* be performed by *all* ANDA applicants and is primarily designed to test for potential chemical degradation during the storage of API. FOF ¶¶ 9, 12. Nowhere in the ICH Guidelines does it state that accelerated stability testing is designed to test for potential *polymorph* instability during API storage. *See* PTX-739.

Indeed, following ICH guidelines, MSN conducted a stability study under accelerated

conditions of 40°C and 75% relative humidity, and found that a chemical impurity developed in its API that was outside of specifications. PTX-194.2; FOF ¶¶ 26-27. To control the impurity, MSN changed the proposed storage conditions for its API from room temperature (~25ºC) to refrigerated (~5ºC). *Id*. This change succeeded in keeping the chemical impurity within specifications in subsequent accelerated testing. *Id*. Exelixis offers no evidence suggesting MSN's API will now experience any chemical instability under the refrigerated storage conditions required by MSN's ANDA.[8]

While Exelixis repeatedly cites this test by MSN as purported evidence that the API is "unstable," Op. Br. at 3, 9-10, 16 n.11, it actually demonstrates the point of accelerated testing. MSN's API showed potential *chemical* instability if stored at room temperature. So, MSN changed its prescribed storage conditions and eliminated the potential for the growth of that chemical impurity. FOF ¶¶ 26-27. And when MSN re-tested its API following ICH Guidelines, the results demonstrated that MSN's API will remain chemically stable during storage. FOF ¶ 27.

Second, even if one accepted that accelerated testing following ICH Guidelines provides some circumstantial evidence of an API's polymorph stability during storage, Dr. Munson applied the *wrong* conditions for MSN's API. FOF ¶ 48. The ICH Guidelines recommend different conditions depending on whether the drug substance or drug product is being tested, and whether

[8] Exelixis wrongly asserts that MSN "continues to struggle with instability," citing counsel's interpretation of an April 2022 Complete Response Letter from FDA requesting MSN investigate a Dimer-2 chemical impurity found in MSN's *Tablets*. Op. Br. at 11, citing DTX-493.1. But this vague claim—which again refers to chemical instability as an implied and unsupported proxy for polymorph instability—has nothing to do with MSN's API. As Dr. Steed—the only witness to address this document—explained, the Dimer-2 chemical impurity is different than the one identified in MSN's initial accelerated testing of its API, discussed above (PTX-739). Tr. 397:22-398:15. And FDA specifically notes that the Dimer-2 impurity is found in the drug *product* but not reported with the drug *substance*, for which FDA had no further questions. DTX-493 at 4; Tr. 398:16-399:6 (Steed).

the sample is intended for storage at room temperature, in a refrigerator, or in a freezer. PTX-739.9-18. For accelerated testing of a drug substance, ICH provides the following guidelines for API stored at room temperature (i.e., the "General case") and in a refrigerator, PTX-739.9-10:

2.1.7.1. General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

2.1.7.2. Drug substances intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

MSN's API will be stored under refrigerated conditions, meaning that, per the ICH-prescribed guidelines, "[a]ccelerated stability is conducted at a temperature of 25°C±2°C and relative humidity 60±5%." DTX-270.27; FOF ¶¶ 26-27. But Dr. Munson did not use those conditions. His accelerated testing was performed at 40°C and 75% relative humidity, which are the conditions recommended for drug substances stored at room temperature.[9] PTX-739.9-10. Thus, because he failed to follow ICH Guidelines, Dr. Munson's testing cannot even reliably predict the chemical stability of MSN's API during storage, let alone its polymorphic stability.

Exelixis argues that the "General Case" is still appropriate for accelerated testing of MSN's

[9] Exelixis also points to Dr. Shah's testimony and its own use of 40°C and 75% relative humidity during accelerated testing of Exelixis's API to justify Dr. Munson's use of the same conditions. Op. Br. at 16. But unlike MSN's API, Exelixis' API is stored at room temperature. PTX-351 at 2. Moreover, Exelixis does not point to any record evidence establishing that Exelixis performed accelerated testing on its API to test for *polymorphic* stability, specifically, during the storage of its API.

API, because the API will eventually be taken out of the refrigerator and formulated into MSN's Tablets, which will then be stored at room temperature. Op. Br. at 17-18. But that is mixing apples and oranges. Exelixis points to no record evidence suggesting—and the ICH Guidelines certainly do not provide—that accelerated testing results meant to predict how a drug substance will behave in storage correlate to how that drug substance will behave after formulated into a drug product. Indeed, that would defeat the very purpose of ICH's separate guidelines for accelerated testing of formulated drug products. *See* PTX-739.9-12 (Section 2.1 Drug Substance), PTX-739.12-18 (Section 2.2 Drug Product). Of course, when Dr. Munson *did* expose MSN's Tablets to the ICH Guideline-prescribed accelerated conditions for drug products stored at room temperature, he did not detect any Form N-2. FOF ¶ 34.

Dr. Munson also deviated from ICH Guidelines in another critical manner. ICH instructs that "stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution." PTX-739.8. Dr. Steed explained this is an important requirement, because accelerated testing "is designed to be a predictor of long-term behavior of the API under the storage conditions." Tr. 334:8-13. Here, Dr. Munson tested MSN's API in "unsealed vials" after removing it from MSN's prescribed container closure system. FOF ¶ 30. This failure to follow ICH Guidelines is particularly glaring because MSN's containers are meant to protect the API during storage from the elevated levels of humidity used by Dr. Munson. FOF ¶ 23. Setting aside the parties' dispute over the relevance of accelerated testing for purposes of an infringement analysis, Exelixis cannot rely on "industry guidelines" to justify Dr. Munson's testing when he has failed to actually follow the guidance upon which he relies.

6. Dr. Munson's Use of Accelerated Conditions for His Infringement Analysis is Not Supported by MSN's Stress Studies

Exelixis' final justification for Dr. Munson's use of accelerated conditions is that MSN subjected its API to elevated temperatures in an open petri dish during a single stress study performed during the development of MSN's Tablets. Op. Br. at 10, 17 (citing DTX-352). But this MSN study was performed at different conditions and for different reasons than Dr. Munson's accelerated testing. FOF ¶¶ 28-29. It does not reflect the conditions to which MSN's commercial API will be exposed and, therefore, cannot support Dr. Munson's infringement analysis.

During its tablet manufacturing process validation, MSN subjected its API to four separate stress tests—pressure, ultraviolet light, elevated temperature, and elevated humidity. Tr. 324:4-21 (Steed); DTX-352; FOF ¶¶ 28-29. Dr. Steed explained that these stress tests were designed to study the API under "various parameters … to see what might happen if the [tablet manufacturing] process went to extreme sets of conditions" before "they finally settle[d] upon the process." Tr. 324:5-9, 400:8-11. Exelixis does not claim that MSN's commercial API will ever be exposed to the collective test conditions of any of these studies.

In the thermal stress test, MSN exposed API to 60ºC in a petri dish in ambient humidity for 24 hours. DTX-352.4-5; FOF ¶¶ 28-29. These conditions differ significantly from the "perfect storm" of Dr. Munson's accelerated conditions, because the stress study did not combine high heat with high humidity for weeks of time. Tr. 325:22-25. Moreover, MSN performed XRPD testing on the API sample after 1, 3, 6, and 24 hours of exposure, and concluded that "the polymorphic form of Cabozantinib, (S)-Malate, Form S, is stable at 60ºC for 24 Hours." DTX-352.4.

Dr. Munson disagreed with MSN's assessment, claiming that "peak changes" could be observed at various points in MSN's diffractogram overlay. Op. Br. at 11, citing DTX-352.5. But Dr. Steed explained that the "minor changes in the width of the peaks" pointed out by Dr. Munson are to be expected. Tr. 326:15-327:7; FOF ¶¶ 29. It is "not unusual for there to be changes in peak

widths as a function of heating, as crystallines move with respect to one another." Tr. 326:15-327:7 (Steed). Critically, Dr. Munson does not claim that he can detect any Form N-2 in MSN's XRPD data. FOF ¶ 29. And Dr. Steed agreed. He concluded that the API's profile is "still Form S" and there is "no evidence of Form N-2." Tr. 326:15-327:7. Exelixis' vague claims that MSN's API is "not stable" are not supported by the record evidence.[10]

7. Use of Accelerated Testing Conditions to Support Infringement Opinions Based on Polymorph Conversion Has Been Rejected

Significant parallels can be seen between this case and *Lundbeck v. Lupin*, which went to trial before Judge Stark last year. 2021 WL 4944963. In that case, plaintiff's expert tested samples of SigmaPharm's API at the storage conditions, as well as after exposure to various other conditions, including 40°C and 75% relative humidity. *Id.* at *98-99. Plaintiff's expert detected no claimed peaks in "untreated," samples, i.e., ones that had not been subjected to accelerated conditions. But after exposing the API for several days (not weeks) to 40°C and 75% relative humidity, the plaintiff's expert then observed the claimed XRPD peaks. *Id.*

Sigmapharm argued "persuasively, that it is the stress tests conducted by" the plaintiff's expert that "intentionally" altered the samples, making the "results unrepresentative" of the product Sigmapharm would actually sell. *Id.* at 99. Notably, Sigmapharm, just like MSN in this case, had its own expert that conducted synchrotron testing and found no signs of the claimed polymorph. *Id.* Nor was there any evidence of the claimed polymorph in Sigmapharm's "proper long-term and accelerated stability studies"—also just like here. *Id.* The Court ultimately found

[10] Even if Form N-2 is a more "stable" polymorph than Form S, as Exelixis claims, Op. Br. 8-9, that relative fact does not move the needle on Exelixis' infringement claim. As Dr. Steed explained, there is nothing inevitable about a less stable polymorph converting into a more stable polymorph under a given set of conditions. Tr. 288:19-289:12. Polymorphic systems have an energy barrier that can prevent conversion from occurring under any meaningful time scale. *Id.* Dr. Steed provided an example of the diamond, which is a less stable polymorph of carbon than graphite, but "of course, we never see diamond converting to graphite on any meaningful time scale." *Id.*

that the accelerated stability studies performed by the plaintiff's expert did not establish infringement against Sigmapharm or any of the other defendants in the *Lundbeck* case. It held that "results Plaintiffs turn to as indicative of infringement [] are not relevant to the infringement analysis" when "they are not representative of the product [Defendants] will sell." *Id.*

Exelixis' argument that *Lundbeck* is "distinguishable" because "the court found . . . 'several overarching deficiencies' not at issue here" (Op. Br. at 23) is unpersuasive. The "overarching" deficiencies noted by Exelixis were applicable to the Court's consideration of infringement against defendants *other than Sigmapharm*. For example, plaintiff's infringement theory rested on the presence of a single peak against Alembic and Zydus, but not Sigmapharm. 2021 WL 4944963 at *94. Plaintiff relied on testing of development batches and/or mishandled samples against Lupin, Zydus, and Macleods, but not Sigmapharm. *Id.* at *95, 98. In plaintiff's case against Sigmapharm, the Court weighed the "actual testing conducted by both sides" as the most "pertinent evidence," and rejected the plaintiff's reliance on accelerated testing as an accurate representation of the product Sigmapharm would sell. *Id.* at 99.

E. MSN Will Not Induce Infringement of Claim 1 of the '776 Patent.

Exelixis concedes that "MSN's proposed label … is immaterial" to inducement, because it will not encourage prolonged exposure of MSN's API to the high heat or humidity required to cause conversion. Op. Br. at 24-25. Instead, Exelixis' sole theory of inducement is that MSN's supply of Tablets will induce "Zydus, healthcare professionals, and/or patients in the United States" to infringe because "Form N-2 is present in MSN's API from the outset." Op. Br. at 24-25. In other words, Exelixis' inducement theory collapses into its direct infringement theory. But as explained above, Exelixis has failed to meet its burden of establishing that Form N-2 is present in MSN's Tablets or API without adulterating them through exposure to conditions that MSN's products will not be subjected to in the real world. Exelixis, therefore, lacks evidence to support a

threshold showing that MSN's Tablets or API directly infringe. *Meyer Intell. Props. Ltd. v. Bodum, Inc.*, 690 F.3d 1354, 1366 (Fed. Cir. 2012) ("a finding of direct infringement is a prerequisite to a finding of inducement"). Further, as Exelixis admits, MSN had no knowledge of potentially infringing use because its internal studies concluded that "Form S is stable under [all] stress study conditions." Op. Br. at 10 (citing PTX-180). *See Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1328 (Fed. Cir. 2009) (finding no inducement where the alleged infringer "knew of its products' *potentially* infringing use") (emphasis added); FOF ¶ 50.

V. CONCLUSION

MSN respectfully requests the Court find Exelixis has failed to meet its burden of proving that making, using, offering to sell, or selling in the United States, or importing into the United States MSN's Tablets or the submission of MSN's ANDA will infringe, and that upon FDA approval MSN will induce infringement of, claim 1 of the '776 Patent.[11]

[11] MSN's Answer also seeks any appropriate relief under 35 U.S.C. § 285. *See* D.I. 9 in C.A. No. 19-cv-02017, Prayers for Relief at G (Nov. 20, 2019). No party has yet made a motion for fees, and, at this point, that issue is premature. MSN may seek fees as permitted by the Federal Rules.

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